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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/721,144	HARIRI, ROBERT J.	
	Examiner	Art Unit	
	Laura M. Mitchell	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6,8,12,13,15-18,20-23,31,32,34-37 and 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6,8,12,13,15-18,20-23,31,32 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

It is noted that claims 1, 18, 31, 34 and 50 have been amended and claims 2, 4, 7, 9-11, 14, 19, 24-30, 33, 38-49 and 51-53 are cancelled in the amendment filed 10/31/2007. Claims 1, 3, 5-6, 8, 12-13, 15-18, 20-23, 31-32, 34-37 and 50 are under examination.

Double Patenting/ Terminal Disclaimer

The terminal disclaimer filed on 11/26/2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 10/366671 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The provisional rejection of claims 1, 3, 5-6 and 18 are on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 10 and 13-14 of copending Application No. 10/366,671 in view of Erices et al (Br. J.

Haematol., 2000 Vol. 109, No.1, abstract) has been overcome by the terminal disclaimer filed on 11/26/2007.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-6, 8, 12-13, 15-18, 20-23, 31-32, 34-37 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection. This rejection is being maintained for reasons of record in the previous Office Action, mailed 6/27/2007 and for reasons outlined below.

Applicant submits that the written description requirement is satisfied where the application "clearly convey[s] the information that an applicant has invented the subject matter which is claimed" and "put[s] the public in possession of what the applicant claims as the invention." MPEP, 8th Edition, Rev. No. 5, § 2163, pg 2100-165.

Applicant submits that the present application as filed describes cytotherapeutic units comprising cells that are $CD34^-$ and $OCT\text{-}4^+$. The specification also teaches that a cytotherapeutic unit can comprise more than one type of potent cell. *See, e.g,*

paragraphs [0040] and [0043], and Example 2. Regarding the cells that may be present in the cytotherapeutic units, paragraph [0040] of the application as published discloses cytotherapeutic units that comprise $CD34^+$ cells, and cytotherapeutic units that comprise $OCT\text{-}4^+$ cells. *See* also paragraph [0011]. Paragraphs [0012] and [0022] of the published application further describe cells, in certain cytotherapeutic units, that "may be characterized by the presence of one or more of the following cell surface markers: $CD10^+$, $CD29^+$, $CD34^-$, $CD38^-$, $CD44^+$, $CD45^-$, $CD54^+$, $CD90^+$, $SH2^+$, $SH3^+$, $SH4^+$, $SSEA3^-$, $SSEA4^-$, $OCT\text{-}4^+$, and $ABC\text{-}p^+$." (Emphasis added.) The present application further describes cytotherapeutic units comprising $CD34^+$ cells at least at paragraphs [0011] and [0040] and in Examples 1-3. Applicant submits that Example 2 describes a cytotherapeutic unit that comprises $CD34^+$ cells and "pluripotential placental cells such as those described in WO 02/064755," which teaches stem cells that are, *inter alia,* $CD34^-$ and $OCT\text{-}4^+$. *See* paragraph [0061]; *see also* paragraph [0043]. Applicant submits that the specification therefore describes cytotherapeutic units comprising both $CD34^+$ cells, as well as $CD34^-$ cells and $OCT\text{-}4^+$ cells, at least some of each of which must be $CD34^-$, $OCT\text{-}4^+$ cells, wherein the cells are obtainable by perfusion. Applicant submits that a person of skill in the art would, therefore, appreciate that Applicant had described, and possessed, cytotherapeutic units comprising $CD34^+$ cells and cells that are $CD34^-$, $OCT\text{-}4^+$.

Applicant's arguments filed 10/31/2007 have been fully considered but they are not persuasive. As discussed in the previous Office Action (mailed 6/27/2007) the paragraphs provided by the Applicant are broad disclosures of a cytotherapeutic unit

comprising at least some potent cells exhibiting CD34, CD8, CD10, OCT4, CD38, CXCR4, or CD117, for example and some embodiments that lack specific antigenic determinants. This does not provide sufficient description of the claimed unit comprising a plurality of cells with the limitation that it comprises $CD34^+$ cells and the specific combination of $CD34^-$ $OCT\text{-}4^+$ cells isolated from postpartum placenta perfusate. The cytotherapeutic unit or library of units as claimed are not disclosed or contemplated in the specification or the examples given. The skilled artisan would not envision a population of potent cells specifically isolated from postpartum placenta perfusate that are $CD34^-$ $OCT\text{-}4^+$ cells from the instant disclosure that provides a list of possible antigenic markers.

Although Applicants point to the specification Example 2 (paragraph 0061) that describes "pluripotential placental cells such as those described in WO 02/064755," which teaches stem cells that are, *inter alia,* $CD34^-$ and $OCT\text{-}4^+$. See also paragraph [0043]. It should be noted that Example 2 does not specifically disclose $CD34^-$ $OCT\text{-}4^+$ cells. In addition WO 02/064755, (8/22/2002, Hariri), discloses embryonic-like stem cells isolated from the postpartum placenta that have multiple cell surface markers (see page 21, lines 8-28. It appears that Applicants intend that the plurality of potent cells comprising $CD34^-$ $OCT\text{-}4^+$ cells isolated from one of a plurality of sources that is postpartum placenta perfusate as part of the cytotherapeutic unit is an essential part of the cytotherapeutic unit.

According to the MPEP 2163.07(b) [R-3], 608.01(p) [R-3] and 37 § CFR 1.57, incorporation of "essential material" by reference may only be done by way of

incorporating by reference of U.S. Patent or U.S. Patent Application Publication. The MPEP defines essential material as material that is necessary to provide a written description of the claimed invention. Since WO02/064755 and WO02/46373 are not U.S. Patents or U.S. Patent Application Publications, they cannot be used to support sufficient written description of the claim limitation of a cytotherapeutic unit comprising $CD34^-$ $OCT\text{-}4^+$ cells that have been isolated from postpartum placenta perfusate.

2163.07(b) [R-3] Incorporation by Reference

Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter. See >37 CFR 1.57 and< MPEP § 608.01(p) for Office policy regarding incorporation by reference.

608.01(p) [R-3] Newly filed applications obviously failing to disclose an invention with the clarity required are discussed in MPEP § 702.01.....While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention. Specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims.

37 § CFR 1.57. Incorporation by reference

(c) " Essential material " may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material " is material that is necessary to:

(1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5-6, 8, 15-18, 20-23, 31-32, 34, 36-37 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fasouliotis et al (2000, of record) in view of Hwang (U.S. Patent Application Pub. No. 2004/0018617, filed 11/4/2002). This is a NEW rejection.

Applicants claim cytotherapeutic units suitable for treatment of a patient in need of hematopoietic cells comprising at least about one hundred $CD34^+$ cells within a plurality of potent cells, the unit comprising cells from a plurality of sources, wherein said plurality of potent cells comprises $CD34^-OCT\text{-}4^+$ cells that have been isolated from postpartum placenta perfusate.

It is noted that the claim is drawn to a product, with a limitation that a subpopulation of the cells have "been isolated from postpartum placenta perfusate" which is a process limitation. Therefore this is considered a product-by-process claim. The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to

prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Fasouliotis et al teach methods of collection and storage of hematopoietic cells for patients with major hematological disorders (i.e. a patient in need of hematopoietic cells). Fasouliotis et al teach methods of collecting cells including collecting umbilical cord blood using a syringe before placental delivery. Fasouliotis et al also teach that cells can be collected by flushing the delivered placenta with saline and retrieving blood by syringe (see pages 15, right column and Table 2 for example), which meets the limitation of a cytotherapeutic unit comprising cells from a plurality of sources wherein one source is the postpartum placenta and postpartum placenta perfusate (e.g. blood and saline) and another source is fetal cord blood.

Fasouliotis et al teach that umbilical cord blood contains about 8,000 erythroid progenitor cells/ml, 13,000-24,000 myeloid progenitor cells/ml and 1000-10,000 multipotent progenitor cells/ml (see page 17, right column, 3rd paragraph, for example). Fasouliotis et al teach that the CD34 antigen is a defining hallmark of hematopoietic stem/progenitor cells and that it is possible to achieve separation of a highly enriched population of $CD34^+$ cells from cord blood using immunoselection (see page 18, left column, 2nd paragraph, for example). Absent evidence to the contrary, the samples taught by Fasouliotis et al would comprise at least about one hundred $CD34^+$ cells and meets the limitation of a cytotherapeutic unit comprising at least about one hundred $CD34^+$ cells. **Fasouliotis et al do not specifically teach that the cells isolated from cord blood or postpartum placenta or postpartum placenta perfusate comprise a subpopulation that is characterized by $CD34^-OCT\text{-}4^+$ markers.**

Hwang teaches somatic stem cells that can be cultured to a phenotype resembling a pluripotent embryonic stem cell. Hwang teaches that these somatic cells can be isolated from human umbilical cord blood, peripheral blood, amniotic fluid and placenta (see paragraphs 0006, 0012 and 0023, for example). Hwang teaches that when these somatic cells are cultured under starvation conditions, they develop a pluripotent phenotype (see paragraph 0007 and 0024). Hwang teaches that the pluripotent phenotype includes characteristic morphology and antigenic properties similar to undifferentiated ES cells. Hwang found that the cells expressed Oct-4, a specific marker for mammalian germ line cells and stem cells. Hwang teaches that the Oct-4 is essential for maintaining the pluripotency of the stem cells (see paragraph

0010, for example). Hwang also teaches that the cells were negative for expression of CD34 and CD45, which suggests that the cells did not belong to cells of a hematopoietic lineage (see paragraph 0025, for example). Hwang teaches that the cells can be used for therapeutic methods including for treating degenerative or inherited diseases or organ replacement. Hwang teach that the somatic stem cells can be isolated from a patient, manipulated if necessary and returned to the original patient and in this way reduce immune rejection that might occur with cells from another individual. Absent evidence to the contrary, at least one of the somatic stem cells taught by Hwang would be isolated by using the method of Fasouliotis et al to isolate cells from umbilical cord blood, postpartum placenta and postpartum placenta perfusate.

It would be obvious to the skilled artisan at the time the invention was made to culture the somatic stem cells under starvation conditions to induce formation of the embryonic stem cell phenotype characterized by $Oct4^+$ expression and $CD34^-$ expression in order to produce cells for the cytotherapeutic unit that are pluripotent because they can be used to treat diseases or to develop into organs (see paragraph 0014 and 0016). The motivation to produce these pluripotent ES like cells from the cells isolated by Fasouliotis et al and include them in the plurality of potent cells for a cytotherapeutic unit is the expected benefit of being able to have cells with an undifferentiated phenotype that are pluripotent and would have low risk of immune rejection as is desired by both Hwang and Fasouliotis et al (see page 14, left column, 2^{nd} and 3^{rd} paragraph, for example). There is a reasonable expectation of success in being able to isolate, and produce pluripotent cells characterized by $CD34^-OCT\text{-}4^+$

markers pattern and include them in a cytotherapeutic unit because they are likely already isolated by the method of Fasouliotis et al and Hwang teaches how to induce pluripotency and a $CD34^-OCT\text{-}4^+$ marker pattern. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore, Fasouliotis et al in view of Hwang render obvious a cytotherapeutic unit suitable for treatment of a patient in need of hematopoietic cells comprising at least about one hundred $CD34^+$ cells within a plurality of potent cells, the unit comprising cells from a plurality of sources, wherein said plurality of potent cells comprises $CD34^-OCT\text{-}4^+$ cells that have been isolated from postpartum placenta perfusate **(claim 1)**.

Absent evidence to the contrary, the erythroid progenitor cells, myeloid progenitor cells and multipotent progenitor cells (see Fasouliotis et al page 17, right column, 3rd paragraph, for example) are pluripotent cells. Hwang teaches that the cells are pluripotent as shown in a teratoma-forming assay (see paragraph 0033-0034), which meets the limitation of a cytotherapeutic unit in which the potent cells are pluripotent cells **(claim 3)**.

Fasouliotis et al teach methods of collecting cells including collecting umbilical cord blood using a syringe before placental delivery. Fasouliotis et al teach that cells can also be collected by flushing the delivered placenta with saline (see pages 15, right column and Table 2 for example), which meets the limitation of a cytotherapeutic unit comprising cells from a plurality of sources wherein one source of cells from the

postpartum placenta, and postpartum placenta perfusate (e.g. blood and saline) and another source is fetal cord blood as claimed in **claims 5-6 and 8**.

Fasouliotis et al teach that immunoselection can be used to separate a highly enriched population of $CD34^+$ cells from the cord blood (see page 18, left column, 2nd paragraph, for example) which meets the limitation of selection of a potent cells to render the unit suitable for therapy for an indicated disease as in **claim 16** and also meets the limitations of **claims 15 and 17** wherein at least one type of cell is excluded or removed from the unit (on the basis of not expressing CD34).

Fasouliotis et al further teach that the hematopoietic cells can be separated based on expression of both CD45RA and CD71 antigens (see page 18, left column, 2nd paragraph, for example), which meets the limitation of the claimed cytotherapeutic unit comprising at least two preselected types of potent cells (**claim 18**).

Fasouliotis et al teach that separation of mononuclear cells from red blood cells (RBC) and polymorphonuclear leukocytes reduces the volume of stored cells and allows the storage of large numbers of cord blood samples in minimal space without the need for freezing un-separated blood bags (see page 16, left column, 3rd-5th paragraphs, for example). The blood sample taught by Fasouliotis et al that has been depleted of RBC and CD34, CD45RA and CD71 selected meets the limitation of a cytotherapeutic unit wherein at least one type of cell and a plurality of cell types (i.e. RBC and any cell not expressing the selected antigenic determinants) have been removed from the unit and anticipates claims **31-32**.

Fasouliotis et al discloses that hematopoietic cell can be obtained from umbilical cord and from a saline perfusion of post partum placenta. Absent evidence to the contrary, at least one of the cell types ($CD34^+$, CD45RA and CD71) would be obtained from the placenta perfusion while at least one of the other cell types would be obtained from the blood from the umbilical cord (i.e. a source of another type) and would meet the limitation of a cytotherapeutic unit comprising mixture of cells from cord blood and $CD34^-OCT\text{-}4^+$ cells isolated from postpartum placenta perfusate (**claim 34**). The $CD34^+$ cells or $CD34^-OCT\text{-}4^+$ cells meet the limitation of **claim 37**, of cells in a cytotherapeutic unit wherein at least one of the cells has been characterized.

Fasouliotis et al teach that the blood samples can be cryopreserved with a cryoprotectant before use (see page 16, right column, 4th paragraph, for example), which meets the limitation of a cytotherapeutic unit in a frozen state and anticipates **claim 36**. Fasouliotis et al teach that large-scale collection and storage of umbilical cord has been established in worldwide umbilical cord blood banks (i.e. libraries). Fasouliotis et al teach that such banks reduce the time from donor search initiation to stem cell acquisition, reduces risks associated with unrelated donor bone marrow transplantation, and could help alleviate under-represented minority donor cell supply (see page 22, right column, 3rd paragraph, in particular). Therefore, the cord blood banks taught by Fasouliotis et al meet the limitation of claim 50 of a library of cytotherapeutic units.

Claims 20-22 are drawn to the cytotherapeutic unit distributed with a certification of the contents of the unit, such as indication of cells excluded or absent from the unit. Claim 23 is drawn to the unit with certification that indicates how the contents of the unit

render it suitable for therapy for an indicated disease or condition. **Claim 50** is drawn to a library of units that have been assayed to ensure the accuracy of the identities and numbers of at least some of the plurality of cells. These limitations appear to be drawn to knowledge concerning the cytotherapeutic unit, wherein the knowledge is certification (e.g. assurance) of the contents of the unit. The identities and numbers of at least some of the cells in the cytotherapeutic unit is an inherent property of the unit. Whether the assay to determine the identities and numbers of the cells is accurate or not is an inherent property of the assay. Absence of particular cell types from a cytotherapeutic unit, whether deliberately excluded or not present to begin with, is an inherent property of the cytotherapeutic unit. In other words, certain cell types are present in the unit or they are not. Either the particular cytotherapeutic unit for an indicated disease state or condition is suitable based on the cell content or it is not suitable. Knowledge or certification of the excluded or absent cells does not alter the properties of the claimed cytotherapeutic unit. Likewise, certification of the suitability of the cytotherapeutic unit does not change the properties of the unit.

> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); see also Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.") See MPEP 2112.

Therefore, the hematopoietic cells in the preparations rendered obvious by Fasouliotis et al in view of Hwang would have numbers and identities, and the assays performed by Fasouliotis et al or Hwang to determine numbers and viability would or would not be accurate. In order for the hematopoietic cell preparations rendered obvious by Fasouliotis et al in view of Hwang to anticipate the claimed cytotherapeutic unit, it is not necessary for Fasouliotis et al or Hwang to have known the identities and numbers of at least some of the plurality of cells or to know or certify the accuracy of the assay. It is not necessary for the Fasouliotis et al or Hwang to specifically certify which cells are absent or have been excluded or whether the preparation of cells or matrix with cells is suitable for treating a subject for the preparation to anticipate the claimed unit. Therefore Fasouliotis et al in view of Hwang render obvious claims **20-23 and 50**.

Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fasouliotis et al (2000, of record) in view of Hwang (U.S. Patent Application Pub. No. 2004/0018617, filed 11/4/2002) in view of Ende et al (Life Sciences 2001, of record). This is a NEW rejection.

Claims 12-13 are drawn to a cytotherapeutic unit wherein said potent cells are obtained from at least two individuals or from at least five individuals.

The teaching of Fasouliotis et al and Hwang are detailed above. Fasouliotis et al in view of Hwang render obvious a cytotherapeutic unit for treatment of a patient in need of hematopoietic cells comprising at least about 100 $CD34^+$ cells within a plurality of potent cells, the unit comprising cells from a plurality of sources, wherein said

plurality of potent cells comprises $CD34^{-}OCT\text{-}4^{+}$ cells that have been isolated from postpartum placenta perfusate. Fasouliotis et al and Hwang do not teach the cytotherapeutic unit wherein said potent cells are obtained from at least two individuals or from at least five individuals.

Ende et al teach a method of pooling umbilical cord samples before administration to reconstitute bone marrow after exposure to radiation. Ende et al discloses that a barrier to use of umbilical cord blood is that it is difficult to obtain enough stem cells for effective grafting especially since adults require many stem cells. Ende et al also discloses an additional difficulty related to variability in the volume and quantity of cord blood samples (see page 1532, 1st paragraph, for example). Ende et al teach that fifteen human umbilical cord blood samples were obtained from full term neonates and that five milliliters of each were mixed in combination with two or three different other specimens (see page 1533, 2nd paragraph, for example). Ende et al teach that combined cord blood samples had an increase in percentage of colony forming units and a significant increase in the number of primitive colonies and $CD34^{+}$ cells when compared to individual samples stored in the same manner (see page 1534, 3rd paragraph and Table 2, for example).

It would have been obvious to the skilled artisan at the time the invention was made to modify the unit rendered obvious by Fasouliotis et al in view of Hwang to incorporate the teaching of Ende et al to use samples of cord blood from two or more individuals to make a cytotherapeutic unit wherein cells are obtained from at least two individuals or at least five individuals because Ende et al discloses that more cells can

be obtained from multiple samples to provide adequate number of stem cells for therapy. The motivation to do so is the expected benefit of as suggested by Ende et al of being able to use cells from at least two individuals or at least five individuals to provide sufficient cells in therapeutic hematopoietic products for all patients, including adults or children of different ethnic origins. There is a reasonable expectation of success in using cells obtained from at least two individuals or at least five individuals because Ende et al teach that there is an increase in cell number after combination of samples and therapeutic hematopoietic products have worked previously as taught by Fasouliotis et al. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore, Fasouliotis et al in view of Hwang in view of Ende et al render obvious a cytotherapeutic unit wherein said potent cells are obtained from at least two individuals (**claim 12**) or from at least five individuals (**claim 13**).

Claim 1, 3, 5-6, 8, 15-18, 20-23, 34- 37 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pykett et al (U.S. Patent No. 6,548,299, of record) in view of Fasouliotis et al (2000, of record) and further in view of Hwang (U.S. Patent Application Pub. No. 2004/0018617, filed 11/4/2002). This is a NEW rejection.

Applicants claim cytotherapeutic units suitable for treatment of a patient in need of hematopoietic cells comprising at least about one hundred CD34+ cells within a plurality of potent cells, the unit comprising cells from a plurality of sources, wherein said plurality of potent cells comprises $CD34^-OCT\text{-}4^+$ cells that have been isolated from postpartum placenta perfusate.

Pykett et al teach a population of cells obtained from blood products comprising hematopoietic cells, including $CD34^+$ cells. Pykett et al teach that the cells can be used to supplement or replenish a patient's hematopoietic progenitor cell population (see column 19, lines 12-25, for example), which meets the limitation of a cytotherapeutic unit suitable for treatment of a patient in need of hematopoietic cells. Pykett et al teach embodiments wherein the hematopoietic cells may obtained from bone marrow, peripheral blood, umbilical cord blood, and placental blood, for example (see column 3, lines 37-50). Pykett et al teach that five to ten milliliters of blood were extracted from an umbilical cord prior to infant delivery. After delivery, the placenta was removed and blood contained in the placenta was collected. Pykett et al teach that the cord blood and placenta blood were mixed together before processing (see column 31, lines 10-25, in particular), which meets the limitation of cells from a plurality of sources wherein one source is fetal cord blood or post-partum placenta. Pykett et al teach an embodiment in which five thousand $CD34^+$ cells are co-cultured with thymic stromal cells and after 7 days, the $CD34^+$ were harvested. Since the culture taught by Pykett et al started with five thousand $CD34^+$ before expansion, absent evidence to the contrary, after harvest there would be at least about one hundred $CD34^+$ cells. **Pykett et al does not teach**

that a source of hematopoietic cells is a postpartum placenta perfusate. Pykett et al does not teach that cells isolated from postpartum placenta perfusate that comprise a population that is characterized by $CD34^{-}OCT\text{-}4^{+}$ markers. Pykett et al does not teach a library of cytotherapeutic units.

The teaching of Fasouliotis et al has been discussed in the above rejection. Specifically, Fasouliotis et al teach methods of collecting umbilical cord blood for storage including collection of the blood using syringes before placental delivery, and optionally flushing the delivered placenta with saline in order to retrieval additional blood (see pages 15, right column and Table 2 for example). Fasouliotis et al teach that a disadvantage of using umbilical cord blood is the relatively low number of nucleated cells in the average donation, and the scarcity of cells potentially limit wide spread therapeutic use of cord blood (see page 18, left column, 3rd paragraph for example). Fasouliotis et al also teach that large scale collection and storage of umbilical cord blood has been established in worldwide umbilical cord blood banks (i.e. libraries). Fasouliotis et al teach that such banks reduce the time from donor search initiation to stem cell acquisition, reduces risks associated with unrelated donor bone marrow transplantation, and could help alleviate under-represented minority donor cell supply (see page 22, right column, 3rd paragraph, in particular). **Fasouliotis et al do not specifically teach that the cells isolated from cord blood or postpartum placenta or postpartum placenta perfusate comprise a subpopulation that is characterized by $CD34^{-}OCT\text{-}4^{+}$ markers**. The teaching of Hwang is detailed above.

It would have been obvious to the skilled artisan at the time the invention was made to perfuse the postpartum placenta as taught by Fasouliotis et al to collect cells for a therapeutic cell composition such as produced by Pykett et al because Fasouliotis et al teach that there is a relatively small number of cells in a sample of umbilical cord blood. The motivation to use postpartum placenta perfusate is the expected benefit of being able to collect additional blood cells as disclosed by Fasouliotis et al (see Table 2, page 15, in particular). There is a reasonable expectation of success in using postpartum placenta perfusate to increase cell number in cytotherapeutic units since it has worked previously as described by Fasouliotis et al.

It would also be obvious to the skilled artisan at the time the invention was made to culture somatic stem cells taught by Hwang under starvation conditions to induce formation of the embryonic stem cell phenotype characterized by $Oct4^+$ $CD34^-$ expression in order to produce cells for the cytotherapeutic unit that are pluripotent because they can be used to treat diseases or to develop into organs (see paragraph 0014 and 0016). The motivation to produce these pluripotent ES like cells from the cells isolated by Fasouliotis et al and include them in the plurality of potent cells for a cytotherapeutic unit is the expected benefit of being able to have cells with an undifferentiated phenotype that are pluripotent and would have low risk of immune rejection as is desired by both Hwang and Fasouliotis et al see page 14, left column, 2nd and 3rd paragraph, for example). There is a reasonable expectation of success in being able to isolate, produce and include pluripotent cells characterized by $CD34^-OCT\text{-}4^+$ markers pattern and include them in a cytotherapeutic unit because they are likely

already isolated by the method of Fasouliotis et al and Hwang teaches how to produce them. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore, Pykett et al in view of Fasouliotis et al in view of Hwang render obvious a cytotherapeutic unit suitable for treatment of a patient in need of hematopoietic cells comprising at least about one hundred $CD34^+$ cells within a plurality of potent cells, the unit comprising cells from a plurality of sources, wherein said plurality of potent cells comprises $CD34^-OCT\text{-}4^+$ cells that have been isolated from postpartum placenta perfusate **(claim 1)**.

Pykett et al teach embodiments wherein the hematopoietic cells are pluripotent or multipotent cells (see column 3, lines 37-50), which meets the limitation of **claim 3**.

Pykett et al teach that the placenta was removed and blood contained in the placenta was collected. Pykett et al teach that the cord blood and placenta blood were mixed together before processing (see column 31, lines 10-25, in particular), which meets the limitation of cells from a plurality of sources wherein one source is fetal cord blood or post-partum placenta (**claims 5-6 and 8**).

Pykett et al teach that the blood products can be fractionated or enriched. Pykett et al teach that the blood was centrifuged to separate mononuclear cells and then remaining erythrocytes were lysed, which reads on exclusion of at least one type of cell from the unit and meets the limitation of **claim 15**. The cell preparation taught by Pykett et al is obtained by separating $CD34^+$ cells from the blood products. Pykett et al teach

that $CD34^+$ cells were isolated using a CD34 progenitor cell selection system comprising mixing the cell sample with anti-human CD34 beads (see column 31, lines 10-40, for example). For example, mature differentiated cells can be selected against or $CD34^+$ cells can be selected from the population of cells by using paramagnetic anti-CD34 beads (see column 12, lines 31-50, for example). Subsequently, the harvested cells were counted, assessed for viability and the presence of CD34 was checked using anti-CD34 antibodies in flow cytometry analysis (see column 33, lines 10-60, in particular) which meets the limitation of a unit wherein cell identities reflect the presence or absence of at least one antigenic determinant (e.g. $CD34^+$), and also selection of the plurality of potent cells to render the unit suitable for therapy for an indicated disease or condition such as a patient with an immunodeficiency (see column 9, lines 20-30 and column 19, lines 12-20, for example) and meets the limitation of **claims 16-17**.

Pykett et al teach that further immunomagnetic methods, using an antibody to the stem cell antigen AC133, were used to select for an immature phenotype of progenitor cells (see column 32, lines 37-59, in particular), which meets the limitation of AC133 is a second preselected type of cell for the hematopoietic population and meets the limitation of a unit with at least two preselected types of cells (**claim 18)**.

Pykett et al teach that the cells can be co-cultured with lymphoreticular stromal cells on a biocompatible matrix in order to expand and direct differentiation of the hematopoietic cells (see column 12, 53-67 lines and column 13, lines 1-11). Pykett et al teach that the lymphoreticular stromal cells can be non-autologous, or from a subject (source) different from the subject (source) of the hematopoietic cells (see column 27,

lines 21-43, for example) and meets the limitation of a cytotherapeutic unit comprising a mixture of cells obtained from umbilical cord blood and $CD34^-OCT\text{-}4^+$ cells isolated from postpartum placenta perfusate, said cells comprising a plurality of different types, at least one of the different types having been obtained from a source that differs from a source of another type and wherein at least about one hundred cells are $CD34^+$ **(claim 34)**. Pykett et al disclose that lymphoreticular stromal cells can be obtained from lymphoid tissue and cryopreserved for later use (see column 14, lines 14-30, for example), which meets the limitation of a cytotherapeutic unit wherein at least one type of cell is frozen separately from another type of cells (e.g. $CD34^+$ cells) and wherein at least one of said cells has been characterized (i.e. is of lymphoid origin) as in **claims 35-36**.

Fasouliotis et al teach that large-scale collection and storage of umbilical cord has been established in worldwide umbilical cord blood banks (i.e. libraries). Fasouliotis et al teach that such banks reduce the time from donor search initiation to stem cell acquisition, reduces risks associated with unrelated donor bone marrow transplantation, and could help alleviate under-represented minority donor cell supply (see page 22, right column, 3rd paragraph, in particular). Therefore, Pykett et al in view of Fasouliotis et al in view of Hwang render obvious claim 50 drawn to a library of cytotherapeutic units.

As discussed above, the identities and numbers of at least some of the cells in the cytotherapeutic unit are an inherent property of the unit. As discussed above, whether the assay to determine the identities and numbers of the cells is accurate or not

is an inherent property of the assay. Absence of particular cell types from a cytotherapeutic unit, whether deliberately excluded or not present to begin with, is an inherent property of the cytotherapeutic unit. In other words, certain cell types are present in the unit or they are not. Either the particular cytotherapeutic unit for an indicated disease state or condition is suitable based on the cell content or it is not suitable. Knowledge or certification of the excluded or absent cells does not alter the properties of the claimed cytotherapeutic unit. Likewise, certification of the suitability of the cytotherapeutic unit does not change the properties of the unit. See MPEP 2112. Therefore, the hematopoietic cell in the preparations rendered obvious by Pykett et al in view of Fasouliotis et al in view of Hwang would have numbers and identities, and the assays performed to determine numbers and viability would or would not be accurate. It is not necessary for the Pykett et al or Fasouliotis et al or Hwang to have known the identities and numbers of at least some of the plurality of cells or to know the accuracy of the assay. Therefore Pykett et al in view of Fasouliotis et al in view of Hwang render obvious claims **20-23 and 50.**

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura M. Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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